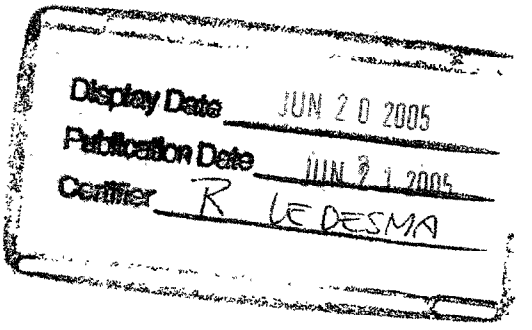

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 2005N–0220]

PDM

Agency Information Collection Activities; Proposed Collection; Comment Request; Current Good Manufacturing Practices and Related Regulations for Blood and Blood Components; and Requirements for Donor Testing, Donor Notification, and "Lookback"

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing an opportunity for public comment on the proposed collection of certain information by the agency. Under the Paperwork Reduction Act of 1995 (the PRA), Federal agencies are required to publish notice in the **Federal Register** concerning each proposed collection of information, including each proposed extension of an existing collection of information, and to allow 60 days for public comment in response to the notice. This notice solicits comments on the information collection requirements contained in FDA's current good manufacturing practice (CGMP) and related regulations for blood and blood components; and requirements for donor testing, donor notification, and "lookback".

DATES: Submit written or electronic comments on the collection of information by [*insert date 60 days after date of publication in the* **Federal Register**].

ADDRESSES: Submit electronic comments on the collection of information to: *http://www.fda.gov/dockets/ecomments*. Submit written comments on the

collection of information to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number found in brackets in the heading of this document.

FOR FURTHER INFORMATION CONTACT: Jonna Capezzuto, Office of Management Programs (HFA–250), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–4659.

SUPPLEMENTARY INFORMATION: Under the PRA (44 U.S.C. 3501–3520), Federal agencies must obtain approval from the Office of Management and Budget (OMB) for each collection of information they conduct or sponsor. "Collection of information" is defined in 44 U.S.C. 3502(3) and 5 CFR 1320.3(c) and includes agency requests or requirements that members of the public submit reports, keep records, or provide information to a third party. Section 3506(c)(2)(A) of the PRA (44 U.S.C. 3506(c)(2)(A)) requires Federal agencies to provide a 60-day notice in the **Federal Register** concerning each proposed collection of information, including each proposed extension of an existing collection of information, before submitting the collection to OMB for approval. To comply with this requirement, FDA is publishing notice of the proposed collection of information set forth in this document.

With respect to the following collection of information, FDA invites comments on these topics: (1) Whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize

the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Current Good Manufacturing Practices and Related Regulations for Blood and Blood Components; and Requirements for Donor Testing, Donor Notification, and "Lookback" (OMB Control Number 0910–0116)—Extension

Under the statutory requirements contained in section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262), no blood, blood component, or derivative may move in interstate commerce unless: (1) It is propagated or manufactured and prepared at an establishment holding an unsuspended and unrevoked license; (2) the product complies with regulatory standards designed to ensure safety, purity, and potency; and (3) it bears a label plainly marked with the product's proper name, manufacturer, and expiration date. In addition, under the biologics licensing and quarantine provisions in sections 351–361 of the PHS Act (42 U.S.C. 262–264) and the general administrative provisions under sections 501–503, 505–510, and 701–704 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 351–353, 355–360, and 371–374), FDA has the authority to issue and enforce regulations designed to protect the public from unsafe or ineffective biological products and to issue regulations necessary to prevent the introduction, transmission, or spread of communicable diseases between States or possession or from foreign countries into the States or possession. The CGMP and related regulations implement FDA's statutory authority to ensure the safety, purity, and potency of blood and blood components. The "lookback" requirements are intended to help ensure the continued safety of the blood supply by providing necessary information to users of blood and blood components and appropriate notification of recipients of transfusion who are at increased risk for

transmitting human immunodeficiency virus (HIV) infection. The public health objective in testing human blood donors for evidence of infection due to communicable disease agents and in donor notification is to prevent the transmission of communicable disease.

The information collection requirements in the CGMP, donor testing, donor notification, and "lookback" regulations provide FDA with the necessary information to perform its duty to ensure the safety, purity, and potency of blood and blood components. These requirements establish accountability and traceability in the processing and handling of blood and blood components and enables FDA to conduct meaningful inspections. The recordkeeping requirements serve preventative and remedial purposes. The disclosure requirements identify the various blood and blood components and important properties of the product, demonstrate that the CGMP requirements have been met, and facilitate the tracing of a product back to its original source. The reporting requirements inform FDA of any deviations that occur and that may require immediate corrective action.

Under the reporting requirements, § 606.170(b) (21 CFR 606.170(b)) requires that fatal complications of blood collection and transfusions be reported to FDA as soon as possible and that a written report shall be submitted within 7 days. Section 610.40(c)(1)(ii) (21 CFR 610.40(c)(1)(ii)) requires each dedicated donation be labeled as required under 21 CFR 606.121 and with a label entitled "INTENDED RECIPIENT INFORMATION LABEL" containing the name and identifying information of the recipient. Section 610.40(g)(2) requires an establishment to obtain written approval from FDA to ship human blood or blood components for further manufacturing use prior to completion of testing. Section 610.40(h)(2)(ii)(A) requires an establishment

to obtain written approval from FDA to use or ship human blood or blood components found to be reactive by a screening test for evidence of a communicable disease agent(s) or collect from a donor with a record of a reactive screening test. Sections 610.40(h)(2)(ii)(C) and (h)(2)(ii)(D) require an establishment to label reactive human blood and blood components with the appropriate screening test results, and, if they are intended for further manufacturing use into injectable products, with a statement indicating the exempted use specifically approved by FDA. Section 610.40(h)(2)(vi) requires each donation of human blood or blood component that tests reactive by a screening test for syphilis and is determined to be a biological false positive be labeled with both test results. Section 610.42(a) (21 CFR 610.42(a)) requires a warning statement, including the identity of the communicable disease agent, on medical devices containing human blood or blood components found to be reactive by a screening test for evidence of infection due to a communicable disease agent(s) or syphilis. Section 610.46(a) (21 CFR 610.46(a)) requires blood establishments to notify consignees, within 72 hours, of repeatedly reactive test results so that previously collected blood and blood components are appropriately quarantined. Section 610.46(b) requires blood establishments to notify consignees of licensed, more specific test results for HIV within 30 calendar days after the donors' repeatedly reactive test. Section 610.47(b) (21 CFR 610.47(b)) requires transfusion services not subject to the Centers for Medicare and Medicaid Services (CMS) regulations to notify physicians of prior donation recipients or to notify recipients themselves of the need for HIV testing and counseling. Section 630.6(a) (21 CFR 630.6(a)) requires an establishment to make reasonable attempts to notify any donor who has been deferred as required by § 610.41 (21 CFR 610.41), or who has been determined

not to be eligible as a donor. Section 630.6(d)(1) requires an establishment to provide certain information to the referring physician of an autologous donor who is deferred based on the results of tests as described in § 610.41.

Under the recordkeeping requirements, section 606.100(b) (21 CFR 606.100(b)) requires that written standard operating procedures (SOPs) be maintained for the collection, processing, compatibility testing, storage, and distribution of blood and blood components used for transfusion and manufacturing purposes. Section 606.100(c) requires the review of all pertinent records to a lot or unit of blood prior to release. Any unexplained discrepancy or failure of a lot or unit of final product to meet any of its specifications must be thoroughly investigated, and the investigation, including conclusions and followup, must be recorded. Section 606.110(a) (21 CFR 606.110(a)) requires a physician to certify in writing that the donor's health permits plateletpheresis or leukapheresis if a variance from additional regulatory standards for a specific product is used when obtaining the product from a specific donor for a specific recipient. Section 606.110(b) requires establishments to request prior Center for Biologics Evaluation and Research (CBER) approval for plasmapheresis of donors who do not meet donor requirements. The information collection requirements for § 606.110(b) are reported and approved under OMB control number 0910–0338 which expires August 31, 2005. Section 606.151(e) (21 CFR 606.151(e)) requires that records of expedited transfusions in life-threatening emergencies be maintained. So that all steps in the collection, processing, compatibility testing, storage and distribution, quality control, and transfusion reaction reports and complaints for each unit of blood and blood components can be clearly traced, § 606.160 (21 CFR 606.160) requires that legible and indelible contemporaneous records of each significant

step be made and maintained for no less than 5 years. Section 606.160(b)(1)(ix) requires a facility to maintain records of notification of donors deferred or determined not to be eligible for donation, including appropriate followup if the initial notification attempt fails. Section 606.160(b)(1)(xi) requires an establishment to maintain records of notification of the referring physician of a deferred autologous donor, including appropriate followup if the initial notification attempt fails. Section 606.165 (21 CFR 606.165) requires that distribution and receipt records be maintained to facilitate recalls, if necessary. Section 606.170(a) (21 CFR 606.170(a)) requires records to be maintained of any reports of complaints of adverse reactions as a result of blood collection or transfusion. Each such report must be thoroughly investigated, and a written report, including conclusions and followup, must be prepared and maintained. Section 610.40(g)(1) requires an establishment to appropriately document a medical emergency for the release of human blood or blood components prior to completion of required testing.

In addition to the CGMPs in part 606 (21 CFR part 606), there are regulations in part 640 (21 CFR part 640) that require additional standards for certain blood and blood components as follows: Sections 640.3(a)(1), (a)(2), and (f); 640.4(a)(1) and (a)(2); 640.25(b)(4) and (c)(1); 640.27(b); 640.31(b); 640.33(b); 640.51(b); 640.53(b) and (c); 640.56(b) and (d); 640.61; 640.63(b)(3), (e)(1), and (e)(3); 640.65(b)(2); 640.66; 640.71(b)(1); 640.72; 640.73; and 640.76(a) and (b). The information collection requirements and estimated burdens for these regulations are included in the part 606 burden estimates, as described in Tables 1 and 2 of this document.

Respondents to this collection of information are licensed and unlicensed blood establishments that collect blood and blood components, including

Source Plasma and Source Leukocytes inspected by FDA, and other transfusion services inspected by CMS. Based on information received from CBER's database systems, there are approximately 81 licensed Source Plasma collection establishments with multiple locations and 1,628 registered Whole Blood collection establishments for a total of 1,709 establishments. There are approximately 2,156 registered blood establishments inspected by FDA. Of these establishments, approximately 773 perform plateletpheresis and leukopheresis. These establishments annually collect approximately 28 million units of Whole Blood, blood components including Source Plasma, and Source Leukocytes and are required to follow FDA "lookback" procedures, and approximately 134 are registered transfusion services that are not subject to CMS's "lookback" regulations. Based on CMS records, there are an estimated 4,980 transfusion services approved for Medicare reimbursement.

The following reporting and recordkeeping estimates are based on information provided by industry, CMS, and FDA experience. Based on information received from industry, we estimate that there are an average of 13 million donations of Source Plasma from approximately 2 million donors and 15 million donations of Whole Blood, including 300,000 (2 percent of 15 million) autologous, from approximately 8 million donors. Assuming each autologous donor makes an average of 2 donations, FDA estimates that there are approximately 150,000 autologous donors.

FDA estimates that approximately 5 percent (12,000) of the 240,000 donations that are donated specifically for the use of an identified recipient would be tested under the dedicated donors testing provisions in § 610.40(c)(1)(ii).

Under § 610.40(g)(2) and (h)(2)(ii)(A), the only product currently shipped prior to completion of testing is a licensed product, Source Leukocytes, used in the manufacture of interferon, which requires rapid preparation from blood. Shipments of Source Leukocytes are preapproved under a biologics license application and each shipment does not have to be reported to the agency. Based on information from CBER's database system, FDA receives an estimated 1 application per year from manufacturers of Source Leukocytes.

Under § 610.40(h)(2)(ii)(C) and (h)(2)(ii)(D), FDA estimates that each manufacturer would ship an estimated 1 human blood or blood component per month (12 per year) that would require two labels; one as reactive for the appropriate screening test under § 610.40(h)(2)(ii)(C), and the other stating the exempted use specifically approved by FDA under § 610.40(h)(2)(ii)(D). According to CBER's database system, there are an estimated 40 licensed manufacturers that ship known reactive human blood or blood components.

Based on information we received from industry, we estimate that approximately 18,000 donations annually test reactive by a screening test for syphilis, and are determined to be biological false positives by additional testing and labeled accordingly (§ 610.40(h)(2)(vi)).

Human blood or a blood component with a reactive screening test, as a component of a medical device, is an integral part of the medical device, e.g., a positive control for an in vitro diagnostic testing kit. It is usual and customary business practice for manufacturers to include on the container label a warning statement that identifies the communicable disease agent. In addition, on the rare occasion when a human blood or blood component with a reactive screening test is the only component available for a medical device that does not require a reactive component, then a statement of warning is required to

be affixed to the medical device. To account for this rare occasion under § 610.42(a), we estimate that the warning statement would be necessary no more than once a year.

Based on information received from industry, we estimate that there are approximately 4,424 repeat donors that will test reactive on a screening test for HIV with 159 confirmed positive. We estimate that each repeat donor has donated two previous times and an average of three components were made from each donation. Under § 610.46(a) and (b), this estimate results in 26,544 (4,424 x 2 x 3) notifications of the HIV screening test results to consignees by collecting establishments for the purpose of quarantining affected blood and blood components, and another 26,544 (4,424 x 2 x 3) notifications to consignees of subsequent test results.

Under § 610.47(b), based also on the information received from industry, we estimate that 80 percent of the 159 (127) confirmed HIV positive were from repeat donors of Whole Blood donations.

Industry estimates that approximately 13 percent of 10 million potential donors (1.3 million donors) who come to donate annually are determined not to be eligible for donation prior to collection because of failure to satisfy eligibility criteria. It is the usual and customary business practice of 1,709 collecting establishments to notify onsite and to explain the reason why the donor is determined not to be suitable for donating. Based on such available information, we estimate that two-thirds of the 1,709 collecting establishments provided onsite additional information and counseling to a donor determined not to be eligible for donation as usual and customary business practice. Consequently, we estimate that only one-third or 570 collection establishments would need to provide, under § 630.6(a), additional information and

counseling onsite to the estimated 433,333 (one-third of 1.3 million) ineligible donors.

It is estimated that another 4.5 percent of 10 million donors (450,000 donors) are deferred annually based on test results. We estimate that currently 95 percent of the establishments that collect 98 percent of the blood and blood components notify donors who have reactive test results for HIV, Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), Human T-Lymphotropic Virus (HTLV), and syphilis as usual and customary business practice. Consequently, 5 percent (85) of the industry (1,709) collecting 2 percent (9,000) of the deferred donors (450,000) would notify donor under § 630.6(a).

As part of usual and customary business practice, collecting establishments notify an autologous donor's referring physician of reactive test results obtained during the donation process required under § 630.6(d)(1). However, we estimate that 5 percent of the 1,628 blood collection establishments (81) may not notify the referring physicians of the estimated 2 percent of 150,000 autologous donors with reactive test results (3,000) as their usual and customary business practice.

The recordkeeping chart reflects the estimate that 95 percent of the recordkeepers, which collect 98 percent of the blood supply, had developed SOPs as part of their customary and usual business practice. Establishments may minimize burdens associated with CGMP and related regulations by using model SOPs developed by industries' accreditation organizations. These accreditation organizations represent almost all registered blood establishments.

Under § 606.160(b)(1)(ix), we estimate the total annual records based on the 1.3 million donors determined not to be eligible to donate and each of

the 450,000 (1,300,000 + 450,000 = 1,750,000) donors deferred based on reactive test results for evidence of infection due to communicable disease agents. Under § 606.160(b)(1)(xi), only the 1,628 registered blood establishments collect autologous donations and, therefore, are required to notify referring physicians. We estimate that 4.5 percent of the 150,000 autologous donors (6,750) will be deferred under § 610.41 and thus result in the notification of their referring physicians.

FDA has concluded that the use of untested or incompletely tested but appropriately documented human blood or blood components in rare medical emergencies should not be prohibited. We estimate the recordkeeping under § 610.40(g)(1) to be minimal with one or less occurrence per year. The reporting of test results to the consignee in § 610.40(g) does not create a new burden for respondents because it is the usual and customary business practice or procedure to finish the testing and provide the results to the manufacturer responsible for labeling the blood products.

The hours per response and hours per record are based on estimates received from industry or FDA experience with similar recordkeeping or reporting requirements.

FDA estimates the burden of this collection of information as follows:

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN[1]

21 CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
606.170(b)[2]	82	1	82	20	1,640
610.40(c)(1)(ii)	1,628	8	12,000	0.08	960
610.40(g)(2)	1	1	1	1	1
610.40(h)(2)(ii)(A)	1	1	1	1	1
610.40(h)(2)(ii)(C) and (h)(2)(ii)(D)	40	12	480	0.2	96
610.40(h)(2)(vi)	1,628	11	18,000	0.08	1,440
610.42(a)	1	1	1	1	1
610.46(a)	1,709	16	26,544	0.17	4,512
610.46(b)	1,709	16	26,544	0.17	4,512
610.47(b)	134	1	134	1	134
630.6(a)[3]	570	760	433,333	0.08	34,667
630.6(a)[4]	85	106	9,000	1.5	13,500
630.6(d)(1)	81	37	3,000	1	3,000
Total					64,464

[1]There are no capital costs or operating and maintenance costs associated with this collection of information.
[2]The reporting requirement in § 640.73, which addresses the reporting of fatal donor reactions, is included in the estimate for § 606.170(b).
[3]Notification of donors determined not to be eligible for donation based on failure to satisfy eligibility criteria.
[4]Notification of donors deferred based on reactive test results for evidence of infection due to communicable disease agents.

TABLE 2.—ESTIMATED ANNUAL RECORDKEEPING BURDEN[1]

21 CFR Section	No. of Recordkeepers	Annual Frequency per Recordkeeping	Total Annual Records	Hours per Record	Total Hours
606.100(b)[2]	249[5]	1	249	24	5,976
606.100(c)	249[5]	10	2,490	1	2,490
606.110(a)[3]	39[6]	1	39	0.5	20
606.151(e)	249[5]	12	2,988	0.083	248
606.160[4]	249[5]	1,928	480,000	0.75	360,000
606.160(b)(1)(ix)	1,709	1,024	1,750,000	0.05	87,500
606.160(b)(1)(xi)	1,628	4	6,750	0.05	338
606.165	249[5]	1,928	480,000	0.083	39,840
606.170(a)	249[5]	12	2,988	1	2,988
610.40(g)(1)	1,628	1	1,628	0.5	814
Total					500, 214

[1]There are no capital costs or operating and maintenance costs associated with this collection of information.
[2]The recordkeeping requirements in §§ 640.3(a)(1), 640.4(a)(1), and 640.66, which address the maintenance of SOPs, are included in the estimate for § 606.100(b).
[3]The recordkeeping requirements in § 640.27(b), which address the maintenance of donor health records for the plateletpheresis, are included in the estimate for § 606.110(a).
[4]The recordkeeping requirements in §§ 640.3(a)(2) and (f); 640.4(a)(2); 640.25(b)(4) and (c)(1); 640.31(b); 640.33(b); 640.51(b); 640.53(b) and (c); 640.56(b) and (d); 640.61; 640.63(b)(3), (e)(1), and (e)(3); 640.65(b)(2); 640.71(b)(1); 640.72; and 640.76(a) and (b), which address the maintenance of various records are included in the estimate for § 606.160.
[5]Five percent of CMS transfusion services and FDA-registered blood establishments (0.05 X 4,980).
[6]Five percent of plateletpheresis and leukopheresis establishments (0.05 X 773).

Dated: 6·14·05

June 14, 2005.

oc05143

Jeffrey Shuren,
Assistant Commissioner for Policy.

[FR Doc. 05–????? Filed ??–??–05; 8:45 am]

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